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Article

Cisplatin and Platinum-Based Chemotherapeutics: Molecular Mechanisms, Clinical Applications, and Emerging Strategies to Overcome Resistance

Ghanem Shaker Aljebouri[1], Andy N.S. Shamaya[2], Malik Jafar Rabea[3], Mustafa S. Al-Timimi[4]

1. Department of Chemistry, College of Science, University of Baghdad, Baghdad, 10071, Iraq
2. Department of Chemistry, College of Science, University of Baghdad, Baghdad, 10071, Iraq
3. Department of Chemistry, College of Science, University of Misan, Amarah, 62001, Iraq
4. Department of Chemistry, College of Science, University of Baghdad, Baghdad, 10071, Iraq

* Correspondence: ghanem.shaker@sc.uobaghdad.edu.iq

Abstract: For nearly half a century, cisplatin has stood as both a beacon of hope and a testament to the enduring struggle against cancer. Discovered serendipitously in the 1960s and granted FDA approval in 1978, this small platinum molecule transformed testicular cancer from a death sentence into a largely curable disease—saving countless young lives and reshaping the landscape of oncology. Yet behind this triumph lies a profound paradox: the very compound that brings healing also inflicts suffering. In response, science has not stood still. Next-generation analogs—carboplatin, oxaliplatin, nedaplatin, lobaplatin—have emerged with gentler toxic profiles, each carrying the legacy of their predecessor while seeking to soften its blows. Nanotechnology wraps the drug in protective carriers, guiding it toward tumors like a letter with a specific address. Combination therapies pair platinum with molecular partners—PI3K inhibitors, PARP inhibitors, immune checkpoint blockers—creating synergies that outsmart resistance. Epigenetic modulators and natural compounds, from curcumin to resveratrol, offer gentler hands to sensitize resistant cells. This review journeys through the molecular soul of cisplatin—from its chemical awakening in aqueous solutions, through its cellular travels and nuclear battles, to the clinical theaters where it saves and harms. We examine the mechanisms that make it work, the resistances that make it fail, and the innovations that seek to honor its legacy while transcending its limitations. For in the end, cisplatin is more than a drug; it is a chapter in humanity's ongoing dialogue with disease—a reminder that even our most powerful medicines carry the weight of compromise, and that the future of cancer care lies not in abandoning such tools, but in refining them with wisdom, precision, and ever-deepening compassion.

Keywords: Cisplatin; platinum-based drugs; DNA adducts; apoptosis; chemoresistance; nanotechnology; combination therapy; cancer chemotherapy

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1. Introduction

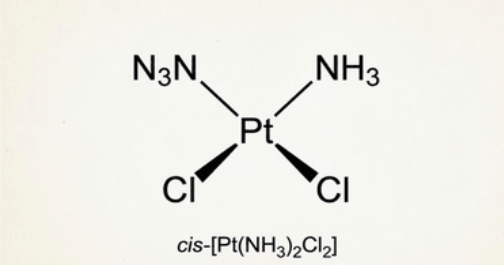

Figure 1. Chemical structure of cisplatin (cis-[Pt(NH3)2Cl2]).

Platinum-based chemotherapeutics have profoundly changed cancer treatment. First discovered by Barnett Rosenberg and colleagues in the 1960s, cisplatin gained FDA approval for the treatment of testicular cancer in males by 1978. The chemical structure of the drug, cis-diamminedichloroplatinum (II) is responsible for the efficacy of the drug against various types of cancers. Unfortunately, the drug suffers from dose-limiting toxicities and a common mechanism of chemoresistance that is shared with other platinum-based drugs [1]. With a desire to circumvent the limitations of the drug, significant research and study are being conducted on the development of next-generation platinum complexes, combination therapies with other drugs, and drug delivery innovations with the goal of improving responses to cisplatin-based chemotherapeutics [2].

This review summarizes current knowledge of cisplatin pharmacology, mechanisms of evasive cisplatin resistance, and different treatment strategies being evaluated to enhance the effectiveness of these valuable chemotherapeutics.

Cisplatin is a neutral square-planar coordination complex with the formula cis-Pt(NH3)2Cl2, with molecular weight of 300.05 g/mol. This aquo-complex reacts with exogenous nucleophiles, and the chloride ligands present on the compound can be displaced by nucleophiles in a chloride dependent activation mechanism. The compound is typically a white to yellow-orange crystalline powder with very poor aqueous solubility (2.5 mg/mL) but is solubilized into an aqueous solution for clinical use, leading to the generation of reactive aquo complexes. The dielectric properties of aqueous solutions lead to the stabilization of intermediates and allow for the mechanism of sequential aquation to occur with great efficiency as typically this would be a slow process [3]. The activation term, which is the nucleophile induced loss of halide leaving group, is favoured by the dielectric timescale at physiological temperatures due to resultant lower entropic barriers. Characterization of peptidic nucleophiles such as cysteine and glutathione shows that they also lose an amine leaving group in the first aquation step leading to formation of the diaqua complex and there are significant variations in the reactivity of the intermediate aquo complexes that leads to substantially different reactivity. In biological systems resulting from high chloride and amino acid concentrations, the aquation mechanism and reactivity of diaqua species exhibit a large dependence on the χ parameter of the leaving ligand which leads to great variations in reactivity profiles. Cisplatin is a β-type soft electrophile becoming activated by nucleophilic displacement as a α-type soft electrophile, usually transiently modifying the soft nucleophile, such as DNA, to adversely affect cellular processes leading to cytotoxic response [4], [5]. The cis configuration of the complex is essential for the antitumor activity of the compound as the trans isomer (transplatin) is less cytotoxic.

2. Materials and Methods

For intravenous formulations of cisplatin, a merit is the stability of the salt under neutral pH, which is desirable for intravenous injection. The photodegradation of cisplatin occurs when the drug is exposed to light. Also, there is trans-isomerization leading to slow inactivation of the drug. The platinum complex is administered in saline solutions (0.9% NaCl) to prevent light absorption. Therefore intravenous formulations of cisplatin must be protected from light during administration. In addition, high concentrations of chloride keep the drug in an inactive dichloro form. The presence of chloride prevents premature aquation leading to the active monoaquated platinum. Consequently, high chloride concentrations prevent premature aquation and minimize local irritation at the injection site, though they do not abrogate the systemic toxicities that manifest following drug distribution

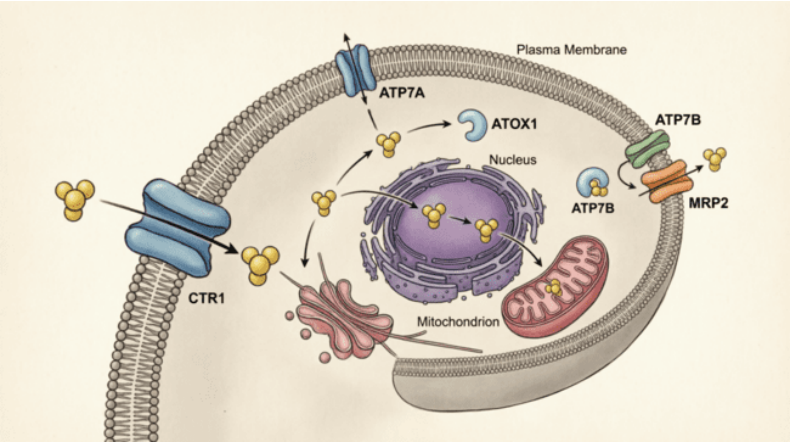

Figure 2. Cellular uptake, intracellular trafficking, and efflux mechanisms of cisplatin.

Cisplatin is a potent chemotherapeutic agent that is actively taken up by cells via several different mechanisms. Roughly 50% of cisplatin drug uptake occurs via the copper transporter 1 (CTR1, SLC31A1) in an energy-dependent, saturable manner. It has been shown that cisplatin-induced cytotoxicity and abortive DNA damage responses are diminished upon CTR1 reduction while increasing CTR1 enhances cisplatin uptake and its subsequent cytotoxicity. SLC31C1 protein expression is reduced in a wide variety of human cancers, and is strongly correlated with cisplatin resistance. Cisplatin uptake also occurs via passive diffusion, organic cation transporters (OCTs) and volume-regulated anion channels (VRAC).

3. Result

The cellular uptake, localization and transport of cisplatin is crucial for its efficacy. Cisplatin is thought to be localized in the nucleus, mitochondria and cytoplasm. Copper chaperones, especially Atox1, promote the movement of platinum species within the cell. The silencing of Atox1 expression was shown to have a tangible effect on the ability of the platinum drugs to accumulate in the nucleus, demonstrating its critical function in targeting of these drugs to their genomic targets [6], [7]. Once in the nucleus, the DNA targets of cisplatin are recognized, leading to the formation of the respective DNA adducts that are associated with cell death and therapeutic efficacy. Concuriously, the reported activity of effluxing platinum drugs by the ATP7A and ATP7B metal export pumps results in not only less drug accumulation in cells, but also less nuclear exposure to the drugs. These events reduce the effectiveness of therapeutic effects of cisplatin. In contrast, other transporters such as the ATP-dependent multi-drug resistance-associated protein MRP2 (ABCC2) are involved in the removal of platinum from the cells [8].

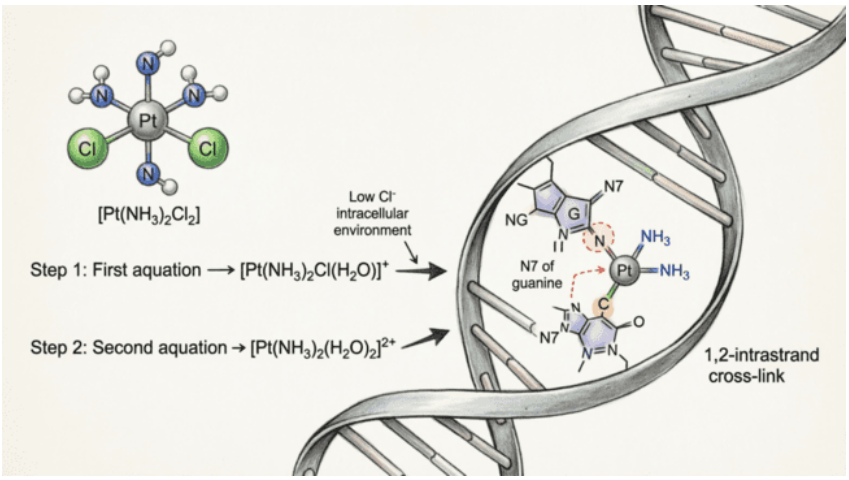

Figure 3. Aquation and DNA binding mechanism of cisplatin leading to 1,2-intrastrand cross-links**.**

Cisplatin, a widely used chemotherapeutic agent for the treatment of numerous kinds of cancer (e.g. testicular, ovarian, lung and bladder carcinomas), is an organo-metallic platinum compound that executes its cytotoxic mechanism by forming covalent adducts with DNA. While these interactions ultimately lead to cancer cell death, the initiation of this pathway requires a series of physical and chemical transformations starting with the drug itself [9], [10]. The active form of cisplatin, unlike the compound as it is administered to a patient which is in a low-chloride environment, is produced by aquation of a cisplatin molecule. Although some aquation is possible in a high-chloride environment, it is greatly facilitated in a low-chloride environment. Subsequently, this active form of the drug targets the most prevalent nucleophilic site in DNA, which is the N7 position of guanine. The primary lesion resulting from this interaction is 1,2-intrastrand cross-links, where two guanines that are adjacent to one another in DNA are covalently bonded to a cisplatin molecule [11]. The highest established of these lesions are 1,2-intrastrand cross-links of d(GpG) (accounting for ~65% of lesions) and less commonly d(ApG) (which constitutes ~25%). These types of lesions introduce structural deformations into DNA, such as bending (ranging from 32-34°) and unwinding (around 13°). The formation of these lesions subsequently leads to significant structural alterations to the DNA double helix. Several High-Mobility Group (HMG) province proteins, such as HMGB-1 and -2, BRCA1 and XPC gene products, recognize these adducts and bind to them leading to recruitment of nucleotide excision repair or homologous recombination proteins for their repair [12]. Failure to recognize and repair these lesions leads to activation of cell-cycle checkpoints, mitotic catastrophe and apoptotic death. Ample examples have been characterized in the literature, indicating that resistance to cisplatin occurs via decreased cellular uptake of the drug, elevated levels of nucleophilic molecules (e.g. glutathione and metallothionein) that sequester cisplatin from DNA, increased expression of efflux transporters, enhanced rate of DNA injury reparation (by nucleotide editing reparation and homologous recombination trails), and failure to trigger checkpoint activation due to altered signalling pathways [13]. In this way, it is clear that recognizing the molecular basis for the DNA adducts of cisplatin is critical to elucidating the mechanism(s) of action for this important chemotherapeutic.

Anticancer drug cisplatin causes damage to DNA, which activates a cellular response. Once DNA damage is recognised, ATM and ATR kinases are activated and these activate checkpoint kinases CHK1 and CHK2. When activated in response to DNA damage, the DNA damage-induced signaling pathways prevent activation of cyclin cyclin-dependent kinases (CDK) to arrest the cell cycle at certain points. Hence, upon DNA damage, CHK1 and CHK2 trigger distinct pathways which arrest the cell cycle at G1/S, intra-S and G2/M checkpoints, respectively, to allow the damaged DNA to be repaired. Upon cisplatin

exposure, ATM activates CHK2, which leads to the inhibition of the cyclin D/CDK4 and cyclin E/CDK2 complexes at G1/S checkpoint [14]. Meanwhile ATR activates CHK1, which signals the inhibition of cyclin A/CDK2 complex at intra-S phase and cyclin B/CDK1 complex at G2/M checkpoint.

p53 is a key mediator of genetic integrity and helps promote survival or cell death in response to DNA damage signaling. Under normal conditions, p53 is inducible and unstable. However, when DNA damage occurs, ATM and ATR activated kinases phosphorylate p53 stabilizing it and activating its target genes that mediate cell cycle arrest, DNA repair, or apoptosis. p53 signaling is important in conferring sensitivity to cisplatin. p53 has been found to induce genes such as p21 which leads to cell cycle arrest. p53 mutations, which are frequently observed in human cancers, are often correlated with resistance to chemotherapy including cisplatin. Cancer cells that have proficient p53 signaling display sensitivity to cisplatin treatment due to the inauguration of p53 genes concerned in cellular mechanisms that promote programmed cell death or cell cycle stem. Conversely, mutations in p53 that abolish its protein functionality renders cancers resistant to cisplatin [15], [16].

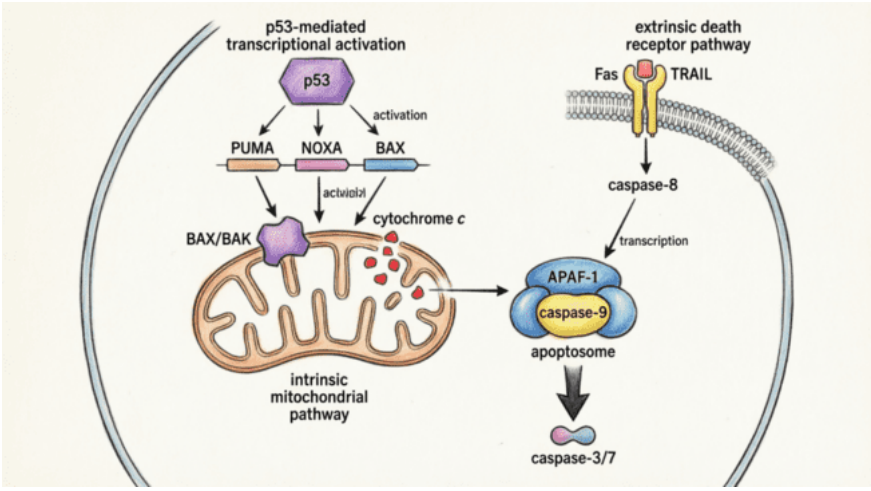

Figure 4. Intrinsic and extrinsic apoptotic pathways activated by cisplatin.

It has been demonstrated that Cisplatin can induce apoptosis, which can be accomplished through both the intrinsic and extrinsic pathways of programmed cell death [17]. The intrinsic pathway is activated by permeabilization of the mitochondrial outer membrane by pro-apoptotic proteins BAX and BAK. Pro- and anti-apoptotic members of the BCL-2 protein family also have a significant role in determining the susceptibility of the cell to apoptosis. Pro-apoptotic proteins that promote cytochrome c release into the cytosol, such as BAD and BIM, are upregulated in response to cisplatin. In contrast, the expression of the anti-apoptotic proteins BCL-2, BCL-XL and MCL-1 are decreased. The net effect will be an increase in pro-apoptotic factors and thus increase the permeability of the mitochondrial outer membrane [18], [19].

An alternative apoptotic signaling pathway is initiated by engagement of death receptors such as Fas (also referred to as CD95) or TRAIL. It is noteworthy that chemotherapeutic agents such as cisplatin can upregulate the expression of Fas ligand thereby sensitizing the tumor cells to the pro-apoptotic signals mediated by the death receptor. Cisplatin can also enhance the ability of tumor cells to undergo apoptosis following activation of TRAIL pathways by upregulating receptors or downstream proteins such as caspase-8. It's important to note that cross-talk exists between the apoptotic pathways, as cisplatin-induced upregulation of death receptors can also promote mitochondrial outer membrane permeabilization by facilitating caspase-8-

dependent cleavage of the BH3-only protein BID, which promotes BAX-dependent apoptosis [20].

Cisplatin is a widely used and well-established DNA damaging agent for cancer treatment (i.e. chemotherapy). However, the effective use of cisplatin is restricted by the acquisition of resistance by cancer cells. A major pathway for resistance to cisplatin is the activation of cell survival pathways. For example, extracellular signal-regulated kinase (ERK1/2), an important MAPK cascade, is a main trigger for cell survival and emergent resistance to cisplatin. On the other hand, c-Jun NH2-terminal kinase (JNK) and p38 MAPK signal mainly mediate apoptosis (death), which is described as the mechanism of action of cisplatin for cancer cell killing [21]. Moreover, MAPK signaling orchestrates diverse cellular outcomes, including survival, resistance, apoptosis, and oncogenes is, etc. First, activated JNK phosphorylates a number of cellular proteins for apoptosis, such as c-Jun, the pro-apoptotic Bcl-2 family member Bim, and p53. Second, p38 MAPK activates p53, which upregulates the pro-apoptotic Bcl-2 family members PUMA and NOXA, leading to the mitochondria-based apoptotic mechanisms. In conclusion, an apparently simple MAPK signaling (JNK or p38 MAPK) may induce a complex array of signals for the genes for apoptosis. To use MAPK signaling for regulating the balance between survival and apoptosis may be a possible way for improvement of effectiveness of cisplatin [22]. Ultimately, the cellular outcome depends on the balance of signaling and the specific context.

Aberrant activation of the PI3K/AKT/mTOR pathway is a major player in development and progression of a wide spectrum of cancers, aiding tumor cell survival even in the presence of chemotherapeutics such as cisplatin. As regards to resistance to existing treatments, it has been shown that the resistance of cancer cells to platinum-based chemotherapy is partly linked to the activation of the phosphoinositide-3-kinase (PI3K)/AKT/mTOR survival pathway [23]. Downstream of binding of ligands to receptor tyrosine kinases (RTKs) like EGFR and Src is the PI3K/AKT/mTOR pathway, which phosphorylates apoptosis-inducing BAD and FOXO. Poor response to platinum compounds is also associated with upregulation of inhibitor of apoptosis proteins (IAPs) including survivin. It has been widely reported that the activation of the PI3K/AKT/mTOR pathway is associated with non-small cell lung cancer (NSCLC), ovarian cancer and head and neck cancers, all of which are resistant to cisplatin. Therefore, the inhibition of the PI3K/AKT/mTOR pathway could be a promising approach to increase the therapeutic response to cisplatin in these cancers [24].

Reactive oxygen species (ROS) levels are increased following treatment with cisplatin due to the oxidative stress induced by the drug. An important source for ROS is the cellular mitochondria, since cisplatin treatments lead to extensive accumulation of the drug in mitochondrial membranes with subsequent inhibition of respiratory chain complexes and disruption of mitochondrial membrane potential ($\Delta\Psi m$) [25]. The accumulation of ROS in mitochondria is associated with increased lipid peroxidation products (e.g., malondialdehyde [MDA] and 4-hydroxynonenal [4-HNE]) as a result of oxidative fatty acid damage in mitochondrial membrane and most likely contributes to mitochondrial DNA damage. Cisplatin-induced oxidative stress can also lead to depletion of glutathione (GSH) and subsequent activation of transcription factors such as Nrf2 and NF-κB, which upregulate antioxidant defenses and anti-apoptotic genes to promote cell survival. This effect is important in the acquisition of chemo resistance since many chemo resistant cells often rely on active antioxidant mechanisms to antagonize the pro-apoptotic effects of anticancer drugs. Thus, oxidation of GSH can lead to activation of Nrf2 and consequent upregulation of genes responsible for preventing undue ROS generation and promote chemo resistance. In addition, mitochondrial oxidative stress and the release of

pro-apoptotic mediators lead to activation of NF-κB and transcription of genes, such as Bcl-2, that are critical in cell survival [26].

As previously mentioned, cisplatin not only acts on DNA but also disrupts calcium homeostasis. Calcium is an important signaling ion in the body and involved in the function of ER and mitochondria. To this point, cisplatin has been shown to induce calcium efflux from the ER and mitochondria which elevates cytosolic Ca^{2+} concentrations. It has also been shown that cisplatin upregulates GRP78/BiP and the subsequent activation of the UPR. This can then modulate whether the cell promotes survival or undergoes apoptosis via CHOP induction [27]. Additional downstream effects of the UPR involved in apoptosis may include caspase-12/-4 which are only present in the ER as well as pro-apoptotic Bcl2 proteins. Calcium-dependent proteases such as calpains may also contribute to the cytotoxic effects of cisplatin as a result of inducing cellular stress.

Cisplatin-based chemotherapy has transformed the prognosis of patients treated for testicular germ cell tumors (TGCT). When compared to other solid tumors of the same age group, the cure rate of TGCT has continued to show striking improvements over the decades, with the most recent reports documenting in excess of 95% cure rates after cisplatin-based chemotherapy in select patients [28]. Therefore, in contrast to all other solid tumors, patients with metastatic TGCT today have a better outcome than patients with local disease. What began with relatively simple, but effective cisplatin-based regimens (that were quickly disparaged by the "rational" chemotherapy community) has matured over the decades into highly coordinated therapy consisting of all the "classic" elements needed to optimize the outcome: multi-drug combinations, dose-intensification strategies (high-dose chemotherapy with stem cell support) for resistant and refractory cases, and state-of-the-art supportive care. Today, cisplatin-based chemotherapy is the cornerstone of both first-line and salvage chemotherapy of patients with metastatic TGCT [29].

Platinum-based chemotherapy is the current standard treatment for epithelial ovarian cancer (EOC), the most common type of gynecological cancer, which continues to be a major obstacle in the development of new effective therapeutics. Based on clinical experience, cytotoxic chemotherapeutic agents, specifically the combination of either cisplatin or carboplatin plus paclitaxel, give response rates between 70 and 80% in patients with EOC. Most patients, however, do eventually go back into relapse with platinum resistant disease, which is a disease that occurs within 6 months of the last platinum treatment [30], [31]. As it is associated with poor overall survival and limited options for further therapy, platinum-resistant disease represents significant unmet need. Delivery of intraperitoneal (IP) cisplatin has been shown to confer survival advantages in some clinical trials. Unfortunately, its clinical use is limited due to its toxicity profile, as well as logistical challenges.

Platinum doublets (cisplatin or carboplatin in combination with either gemcitabine, paclitaxel, docetaxel, pemetrexed, or vinorelbine) are standard first-line treatment for advanced non-small cell lung cancer, and showed modest survival benefits in the adjuvant setting post-surgery [32]. For small cell lung cancer, platinum doublet cisplatin in combination with etoposide is the standard first-line therapy. This regimen faces significant challenges of resistance, particularly in the case of advanced stages or after multiple chemotherapy cycles; in this situation, cisplatin resistance is recognized as a crucial factor in the failure of treatment.

The mechanisms of cisplatin resistance are complex: cancer cells undergo metabolic reprogramming, which promote the activation of signaling regulatory networks and allow the cancer cells to acclimate to cisplatin [33]. The acquisition of cisplatin resistance

is furthermore associated with enhanced epithelial-mesenchymal transition and the acquisition of stem cell-like properties.

Head and neck squamous cell carcinoma (HNSCC) is an aggressive malignancy for which cisplatin-based concurrent chemoradiotherapy remains the standard of care. However, this approach is associated with significant toxicities, including mucositis, dysphagia, and nephrotoxicity, which substantially limit its tolerability [34]. The EXTREME regimen — combining cisplatin, 5-fluorouracil, and the epidermal growth factor receptor (EGFR) inhibitor cetuximab — is recommended for recurrent or metastatic HNSCC with suboptimal response to first-line therapy. Notably, immune checkpoint inhibitors are progressively replacing conventional chemotherapy in molecularly selected patient populations

Cisplatin is an effective drug against cancers of the urothelium (bladder cancer), gastric cancer, cervical cancer, and osteosarcoma. In patients with muscle-invasive bladder cancer, neoadjuvant cisplatin-based chemotherapy (MVAC, GC) results in improved response rates and survival [35]. The combination of cisplatin used with radiotherapy for the treatment of cervical cancer is a standard treatment. Landmark trials have shown survival benefits by adding cisplatin-based chemotherapy. In parallel, a wide range of cisplatin-based combinations have been studied in the advanced gastric cancer setting (especially for the NEPA trial results) and significant survival improvements have been reported. As summarized here, cisplatin has played a major role in the standardization of both cisplatin plus radiotherapy and cisplatin-based combinations for the treatment of these cancers. Platinum's status as a valuable and nearly mandatory drug has been clarified [36].

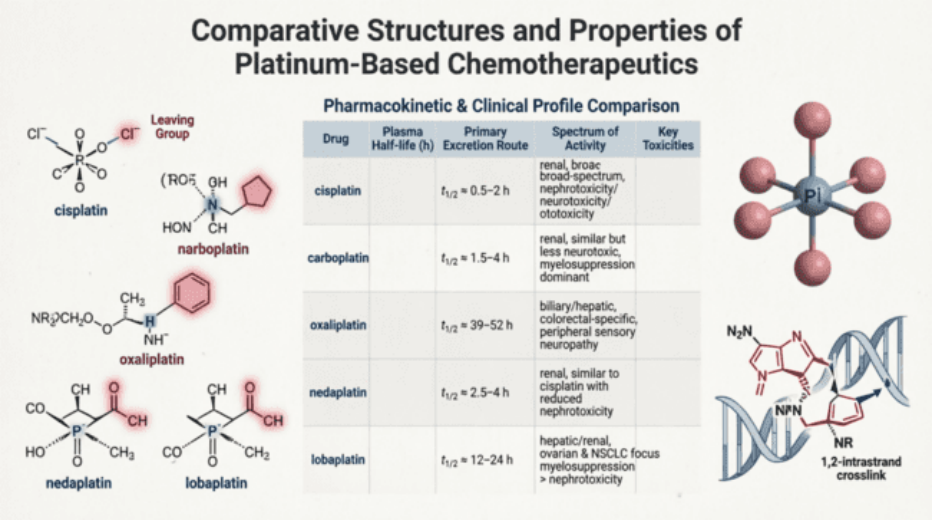

Figure 5. Comparative structures and pharmacological properties of platinum-based chemotherapeutics.

Carboplatin Unlike the first-generation platinum compound cisplatin, which entered clinical use in the mid-1970s, carboplatin (a second-generation platinum analog with a cyclobutanedicarboxylate leaving group) has a reduced chemical reactivity and slower DNA binding kinetics, leading to the development of an improved safety profile [37]. In particular, carboplatin has shown minimal nephrotoxicity, neurotoxicity and emetogenic potential compared to cisplatin; however, it can result in a more pronounced myelosuppression (thrombocytopenia). Carboplatin is eliminated renally, which presents a unique practical issue where dose adjustment must occur based on the amount of drug cleared via glomerular filtration [38]. The equation most often used to determine the dosing of carboplatin is the Calvert formula:

Carboplatin dose = (target AUC) x (GFR + 25).

The formula is particularly helpful regarding carboplatin's safety profile; the dose intensity at which the drug becomes efficacious relative to its side effect profile can be controlled via the adjustment of glomerular filtration rate (GFR) and target area under the curve (AUC).

Oxaliplatin The third generation diaminocyclohexane platinum complex, oxaliplatin, is the backbone of our treatment approach for colorectal cancer in combination with 5-fluorouracil/leucovorin (the FOLFOX combination). The two most important positive features of oxaliplatin are that it has a unique spectrum of activity and that it has proven to be effective in patients with colorectal cancer where cisplatin and carboplatin have not been very effective until now [39], [40]. Among some of the important side effects of oxaliplatin is the induction of dose-limiting neurotoxicity, which is characterized by acute and chronic peripheral sensory neuropathy, but differs considerably from the neurotoxicity of cisplatin.

Nedaplatin and **Lobaplatin** The introduction of drugs with lower resistance and lesser toxicity has led to the surging popularity of platinum drugs as highly effective chemotherapeutic agents. Novel groups of investigational platinum compounds have been continuously tested in Asia as third-generation analogs of cisplatin and carboplatin due to nephrotoxicity and other adverse effects not exhibited. In this chapter, we will describe several third-generation platinum compounds that have been developed in Asia and are imminent for clinical applications. Nedaplatin has a markedly reduced nephrotoxicity and has been authorized for the remedy of head and neck, lung, and esophageal diseases only in Japan. Another newly developed compound, Lobaplatin, has also displayed activity in treating human breast cancer and chronic myelogenous leukemia with a more favorable toxicity profile and a significantly lesser degree of renal and neural toxicity [41], [42].

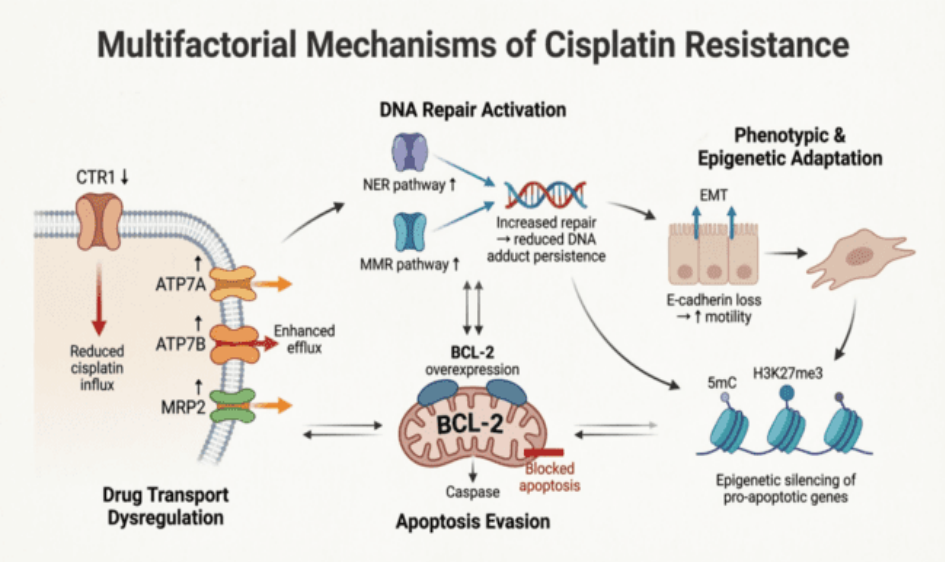

Figure 6. Multifactorial molecular mechanisms underlying cisplatin resistance.

Cisplatin resistance has been a challenging obstacle in the treatment of various cancer types. Different resistance mechanisms are identified, of which the decreased accumulation of cisplatin is the most studied mechanism to date. This decreased accumulation can take place through the downregulation of its main uptake transporter CTR1 through either a mutation or mislocalization of the protein. Other mechanisms of reduced accumulation involve the efflux transporters ATP7A and ATP7B, which cooperate to sequester and export platinum species from the cytoplasm [43]. Besides reducing the accumulation of the drug, these, as well as the fourth major reduction route, its binding with sulfur-containing biomolecules, also led to the destruction of the drug's

biological function. Some of the main sulfur-containing biomolecules associated with resistance are metallothioneins (MTs) and glutathione (GSH), which sequester platinum species to prevent it from damaging nuclear DNA [44].

Cisplatin induces bulky DNA adducts that are primarily removed by the nucleotide excision repair (NER) pathway. Overexpression of NER components, including ERCC1, XPF, XPG, and XPA, has been consistently linked to cisplatin resistance [50]. The mismatch repair (MMR) system, encompassing MSH2 and MLH1, recognizes cisplatin-induced DNA lesions and participates in downstream signaling that promotes cytotoxicity [45]. Deficiency in MMR components paradoxically correlates with platinum sensitivity in certain contexts, owing to the accumulation of unrepaired damage and enhanced immunogenicity; however, in ovarian, lung, and testicular cancers, complex compensatory mechanisms may ultimately confer resistance despite initial MMR impairment [46].

Epithelial-mesenchymal transition (EMT) is a biological process with important implications for cancer cell behavior and drug resistance, through mechanisms that remain poorly understood. One feature of this biological process is the loss of epithelial features, resulting in down-regulation of the epithelial marker E-cadherin and up-regulation of vimentin and N-cadherin. Furthermore, the activation of specific transcription factors involved in EMT (such as Snail, Slug, Twist, and ZEB1) is linked to the induction of several cellular events such as changes in drug resistance, decreased growth and increased survival signalling [47]. In addition to intrinsic mechanisms, resistance is thought to be facilitated by the tumor microenvironment (e.g. tumor-associated fibroblasts, or CAFs; tumor-associated macrophages, or TAMs; and hypoxia).

Cisplatin-resistant cells undergo profound metabolic adaptations, shifting from glycolysis toward oxidative phosphorylation to meet elevated ATP demands [48]. Enhanced glutamine metabolism fuels mitochondrial respiration, while constitutive activation of the Nrf2-ARE pathway bolsters antioxidant defenses, enabling survival under persistent oxidative stress [49]. Elevated lactate production not only supports bioenergetic requirements but also remodels the tumor microenvironment to facilitate immune evasion. Collectively, these metabolic alterations confer a robust survival advantage, allowing resistant cells to withstand therapeutic pressure [50].

Resistance to apoptosis in cancer cells can occur through several different mechanisms. Adaptive evasion of apoptosis allows tumor cells to overcome therapeutic-induced apoptosis. As cells become resistant to chemo- and/or radiotherapy, they can acquire mutations that benefit their survival. In response to apoptosis-inducing therapy, cancer cells can up-regulate anti-apoptotic BCL-2 family members (BCL-2, BCL-xL, and MCL-1), as well as inhibitors of apoptosis proteins (cIAP1, cIAP2 and XIAP), and pro-survival kinases (AKT and ERK), which aid in their survival [51], [52]. Alternatively, tumor cells can develop genetic alterations that compromise the pro-apoptotic arm (mutations/inactivation of p53, loss of pro-apoptotic BAX and/or BAK). Other acquired features of apoptosis-resistant tumor cells can be identified as well, including altered expression of death receptors.

Cisplatin is a common drug used in the treatment of various cancers due to its ability to induce DNA damage. However, tumors become resistant to cisplatin over time, which leads to the failure of chemotherapy [53]. Hence, it is important to understand the molecular methods underpinning this form of drug opposition that would help increase treatment efficacy and efficiency.

The developments of current research indicate that epigenetic changes serve an important role in acquired cisplatin resistance. In particular, dysregulation of the following epigenetic alterations container consequence in the happening of drug-resistance in cancer:

a. DNA methylation
b. histone modifications

c. dysregulation of miR-21, miR-155 (promote resistance; target tumor-suppressive PTEN, PDCD4)
d. dysregulation of lncRNA, circRNA

Cisplatin-resistant cells exhibit distinct phenotypic alterations compared to their parental sensitive counterparts [54]. For instance, the expression of tumor-suppressive miRNAs (miR-34a, miR-200 family) is downregulated in resistant cells.

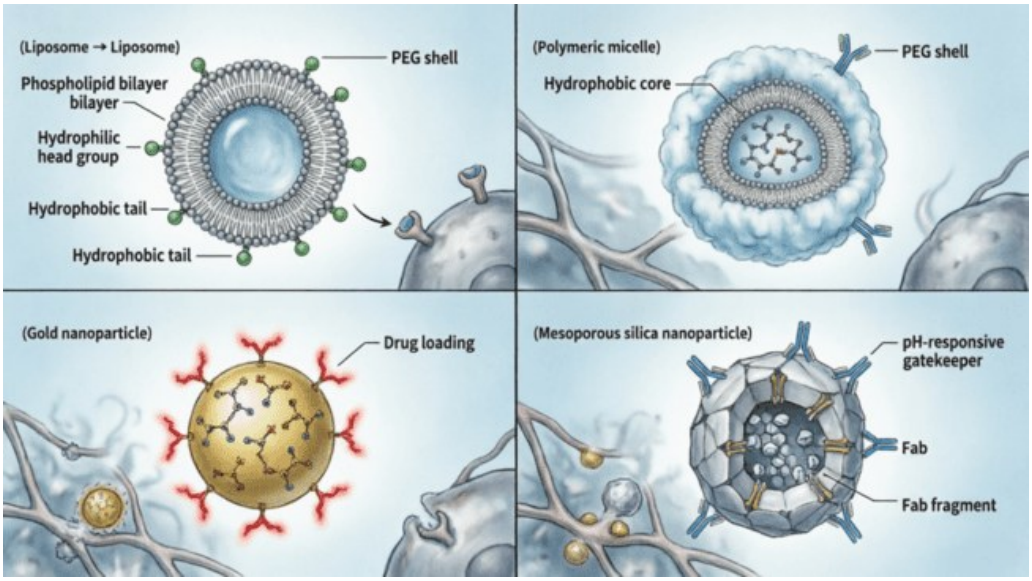

Figure 7. Nanotechnology-based cisplatin delivery systems including liposomes, micelles, and nanoparticles.

A number of nanoparticle formulations have been developed to enhance cisplatin, with better pharmacokinetics, tumor targeting and improved toxicity profiles. For example, Lipoplatin™, a liposome-based formulation, reduces toxicity and increased effectiveness of cisplatin via the enhanced permeability and retention (EPR) effect and is currently in clinical trials. Other strategies include polymeric micelles, gold nanoparticles, mesoporous silica nanoparticles, and carbon nanotubes [55]. These nanoparticles can also be incorporated with drugs for controlled release. This controlled release can be tuned by particle size, shape, charge, or surface chemistry, and by the selection of targeting ligands such as folate, transferrin, antibodies, and peptides.

Table 1. Comparison of Nanotechnology-Based Cisplatin Delivery Systems

Nanocarrier Type	Advantages	Limitations	Clinical Status
Liposomes	Biocompatible, EPR effect, reduced toxicity	Low drug loading, stability issues	Phase II/III trials
Polymeric micelles	High drug loading, tunable release	Polymer-related toxicity	Preclinical/Phase I
Gold nanoparticles	Surface functionalization, imaging capability	Long-term biocompatibility concerns	Preclinical
Mesoporous silica	High loading capacity, controlled pore release	Potential silica toxicity	Preclinical
Carbon nanotubes	Unique cellular uptake, high surface area	Biodistribution concerns	Early preclinical

Both classical and novel therapies have been synergistically combined to overcome tumorigenesis and resistance mechanisms affecting their anticancer efficacy. Rational combination strategies include PI3K/AKT/mTOR inhibitors (everolimus, MK-2206), PARP inhibitors for BRCA-mutated cancers, anti-angiogenic agents (bevacizumab), and immune checkpoint inhibitors (pembrolizumab, nivolumab), with platinum chemotherapy for synchronous targeting and improved efficacy [56], [57]. The combination of immune checkpoint inhibitors with platinum chemotherapy for enhanced efficacy has been firmly established as the new standard of care for squamous cell carcinoma of the head and neck (HNSCC) and non-small cell lung cancer (NSCLC).

Epigenetic alterations impose transcriptional modifications on genes that lead to tumorigenesis. Therapeutic strategies targeting these epigenetic alterations have been explored in cancer treatment. Specifically, epigenetic inhibitors have been employed to restore inhibitory tumor suppressor function and promote platinum sensitivity [58].

The use of various epigenetic inhibitors such as histone deacetylase inhibitors (HDACi), DNA methyltransferase inhibitors (DNMTi) and bromodomain inhibitors have been exploited as potential compounds to enhance the efficacy of platinum-based agents. HDACi vorinostat and panobinostat have been found to enhance cisplatin-induced DNA damage and apoptosis by promoting changes in chromatin accessibility through the modulation of DNA repair protein expression.

Emerging data on the use of natural compounds that can enhance the effectiveness of chemotherapeutic agents have received considerable attention by researchers, allowing for the exploration of "nutraceuticals" or "functional foods" as adjuvants to the current conventional medicines [59]. These naturally occurring products have wide-ranging chemosensitizing properties that can modulate various resistance pathways including those regulated by Nrf2, NF-κB, PI3K/AKT, and apoptotic signaling.

Natural compounds such as curcumin, resveratrol, EGCG, and berberine are a few examples of some of the naturally occurring products that are being explored as adjuncts to platinum chemotherapy currently administered in the clinical setting in order to enhance the efficacy of the chemotherapeutic agents while allowing for mitigation of potential toxicity normally associated with platinating agents [60].

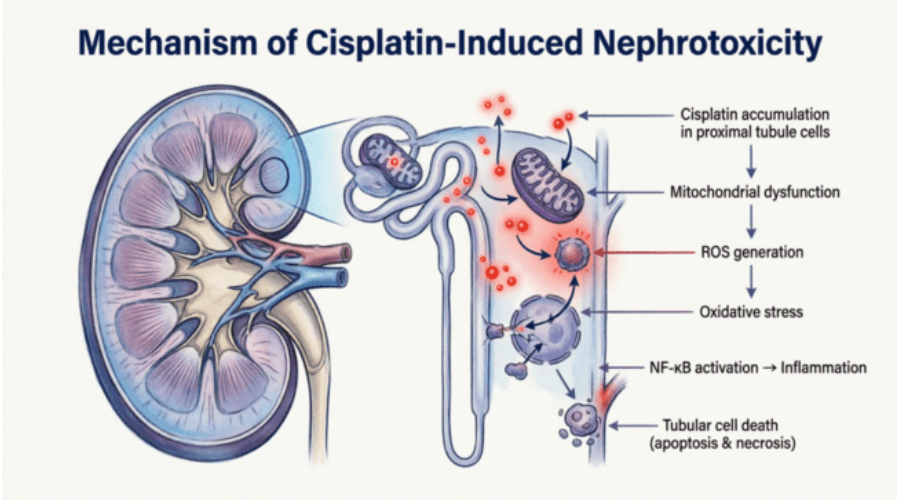

Figure 8. Mechanism of cisplatin-induced nephrotoxicity in renal tubular cells.

Acute kidney injury (AKI) is a significant toxicity of cisplatin, occurring in 20–30% of patients treated with this chemotherapeutic agent due to its damaging effects on renal tubules. Studies indicate that the mechanisms underlying cisplatin-induced AKI include mitochondrial dysfunction, oxidative stress, inflammation and apoptosis resulting in tubular cell death. Although several preventive strategies for cisplatin-induced

nephrotoxicity have shown promise in clinical trials, none have been universally adopted as standard of care [61].

Preventive strategies for cisplatin-induced nephrotoxicity include aggressive intravenous hydration prior to cisplatin infusions (2–3 L/day), magnesium supplementation and avoidance of nephrotoxic co-medications if possible. Amifostine, a radical scavenger that selectively targets normal tissues, has shown promise with protective effects against nephrotoxicity but the practical utility of this drug is limited due to side effects including hypotension and nausea [62].

4. Discussion

Cisplatin is a chemotherapeutic agent for the treatment of various tumors, including those affecting the head and neck, lungs, ovaries, and testes. Its adverse effects are broad, with peripheral sensory neuropathy being one of the most troublesome. Symptoms manifest as paresthesia, numbness, and a loss of proprioception, resulting in instabilities in walking and, in severe cases, a foot drop. The continued use of cisplatin to treat cancer is accompanied by an additional risk. Neurotoxicity from cisplatin can lead to irreversible effects, such as sensory deficits, which accumulate over time. This accumulation occurs because cisplatin preferentially accumulates in the dorsal root ganglia, inducing mitochondrial dysfunction, which in turn leads to axonal degeneration, cellular death, and therefore sensory deficits [63]. Management strategies include the administration of neuroprotective agents such as glutathione, vitamin E, and acetyl-L-carnitine, as well as dose modification.

Pediatric patients treated with a widely used chemotherapy agent, cisplatin, are at risk for high-frequency sensorineural hearing loss that can affect up to 60% of treated patients. Hearing loss is particularly concerning in pediatric populations due to potential long-term impacts on socialization and education. Cisplatin damages cochlear outer hair cells through generation of reactive oxygen species (ROS) that activate inflammatory cascades, leading to loss of hearing [64], [65], [66]. To counteract these effects, the FDA-approved otoprotectant sodium thiosulfate, when given before cisplatin, neutralizes the injurious effects of cochlear ROS while preserving the systemic antitumor activity of the chemotherapy agent.

Severe nausea and vomiting, though historically debilitating, are now largely preventable with modern antiemetic regimens. The combination of a 5-HT_3 receptor antagonist, NK_1 receptor antagonist (aprepitant), and dexamethasone provides excellent control for acute and delayed emesis [67], [68].

Cisplatin causes moderate myelosuppression (anemia, neutropenia, thrombocytopenia), which is generally less severe than with carboplatin. Hypomagnesemia, hypokalemia, and hypocalcemia are common electrolyte disturbances requiring supplementation. Cardiotoxicity (arrhythmias, ischemia, heart failure) and hepatotoxicity are less common but clinically significant in susceptible populations [69].

5. Conclusion

Cisplatin is one of the most widely used antitumor drugs in oncology, responsible for the curative treatment of testicular cancer and palliative efficacy in multiple malignancies. Cisplatin is extremely effective in inhibiting the proliferation of malignant cells, but the adverse effects of high-dose cisplatin, together with the development of multidrug resistance, limit its clinical application. Future research should focus on improving the efficacy and safety of cisplatin. The use of tumor-specific nanocarriers for the delivery of cisplatin is an elegant approach, mimicking biological targeting mechanisms. Predictive biomarkers that forecast tumor response could serve as powerful tools to enhance the efficiency of cisplatin therapy. At present, the most promising candidates include ERCC1 (excision repair cross-complementation 1), BRCA1/2 and CTR1 (copper transporter 1). Thus, future research should focus on the targeted delivery of cisplatin to the malignancy by employing novel tumor-specific nanocarriers, the identification of new biomarkers that

guide patient-specific chemotherapy clinical decisions, the design of new combination regimens that include different molecules for inhibiting protein kinases or for preventing the cellular efflux of cisplatin, and the use of pharmacogenomics strategies for predicting the response of unique patients to the specific strategies, representing the main future path of investigation. Despite the numerous preclinical studies, nanotechnology solutions still show incomplete clinical efficiency and toxicity, but they have the potential to become an innovative and efficient treatment modality in the management of various tumors. By improving the efficacy of established therapies, such as cisplatin, the new strategies, including nanotechnology, immunotherapy and precision medicine, will ultimately result in improved survival rates and reduced toxicity.

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